

## New Center to Study Environmental Impacts on Reproductive Risk

Living in North Carolina, where thousands of Persian Gulf War veterans returned after their service overseas, NIEHS geneticist Mike Shelby was exposed to a media blitz of press reports linking—or at the other end of the spectrum, completely discounting a link—chemical exposures of Gulf War veterans and birth defects among their children. “The evidence is very weak, but the pop press tends to sensationalize even the slightest risk because that sells better than hardcore interpretations that include uncertainties and caveats,” says Shelby. Concerned about what he felt was an uninformed controversy that arose on this issue, Shelby began formulating an idea for a way to improve the body of knowledge available on reproductive risks from environmental exposures.

Shelby contends that a major problem behind sensational, if inaccurate, media reports is that the state of the science in reproductive risk is, at best, uncertain. The press and the public may be left to draw their own conclusions about why more than 20% of couples can’t conceive a child, and more than two-thirds of all birth defects are without definable cause. Diane Aronson, director of Resolve, an infertility support organization, echoes the problem: “Tell me what to say to those men and women who want so desperately to have a healthy child, and who think it is the air they breathe or the water they drink that prevents them.”

Shelby is calling for the establishment of a scientific clearinghouse of sorts that will produce balanced assessments of the adverse effects of chemical exposure to environmental toxicants on all aspects of reproduction, including genetics, fertility, and development. “Somewhere there must be a voice of reason, a respected source from which objective, balanced answers to such questions are available,” says Shelby. “The public supports our research and testing activities and deserves informed answers to their questions. Such answers must be based on what we know, and equally importantly, what we don’t know. What we don’t know needs to be made clear so that, when appropriate and feasible, studies can be conducted to fill these knowledge gaps.”

The Center for the Evaluation of Risks to Human Reproduction would be based somewhat on the model of the International Agency for Research on Cancer (IARC), which uses groups of scientific experts to develop monographs on human carcinogenic risks. The center, which would be funded by a consortium of federal agencies and private industries, would be an independent organization, staffed by toxicologists and support personnel who would arrange meetings of expert committees, and prepare, publish, and distribute reports. Topics for evaluation would be selected by an oversight committee designated by those contributing support. Unlike the IARC, however, no defined categories of evidence of effects are envisioned for the reproductive risk center, says Shelby.

Shelby is now working with the NIEHS grants program to determine how the center can move from a proposal to a reality. He estimates the institute will publish a request for proposals for establishment of the center by September, which means the center could exist as soon as late 1997. The NIEHS will choose the proposal and act as an administrator for the center.

Although it will take time to get the center up and running, Shelby insists that the public must have such a resource. “We have to have fair reporting, so the public isn’t continually worried about things that maybe they shouldn’t be, or sanguine about what may be real risks,” he says. “People are more concerned about the health of their children, or even their ability to have a family, than anything else—including cancer.”

### An Idea Whose Time Has Come?

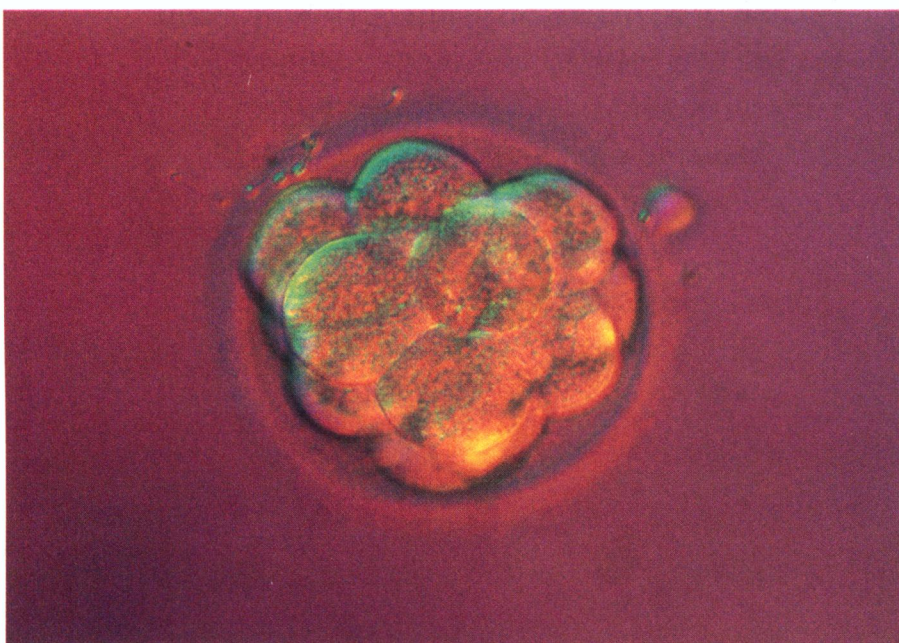
The idea for such a center is not new and, in fact, already has a history of both failure and limited success. It is a concept that can be problematic in its execution and in its acceptance by both scientists and journalists.

Bernard Schwetz, director of the National Center for Toxicological Research, originated the idea for such a study center a decade ago at the NIEHS, but the idea didn’t fly, he says, because the NIEHS “did not consider itself a risk assessment agency.” But now it might work, Schwetz maintains, in part due to the idea that “there needs to be consistency in this important field.” Schwetz believes such a center would present an opportunity to help make an impact on public health: “I know how sizeable a disease load there is in humans in the reproductive area. If we helped develop the data to understand these problems better, some of it may be preventable.”

In fact, a prototype of a reproductive toxicology assessment center was successfully launched in 1989 by the Institute for Evaluating Health Risks (IEHR). Its director, John Moore, gathered funding from a mix of federal agencies and industries and assembled a dozen experts to focus risk assessment where it is most needed.

As Moore, a former EPA administrator and deputy director of the National Toxicology Program, sees it, “people are uncomfortable with the dogmatic way that risk pronouncements are made. It has all evolved to a yes–no type of decision. If yes, it is then translated into an arcane gobbledey-gook threshold number, which everyone then becomes a slave to.”

In developing the IEHR evaluative



Reproductive Biology Associates

**Impact on embryos.** A new NIEHS center will evaluate the effect of environmental agents on reproductive risks.



process, Moore's group first wrestled with the issue of balancing bias—of experts clearly stating their opinions, and then working toward consensus. The group also tackled the problem of how to quantitatively express exposures in the context of a dose that may cause adverse effects. However, the core of their activity “looked at all human and animal data to first come up with a ‘sufficiency’ type of judgment. Then we went into the general toxicology database to look at types of effects and consistency of those effects. These data sets were then integrated to come up with a statement that expresses a judgment as to the composite data's relevance to humans,” says Moore.

The group has already published one paper on the effects of lithium on reproduction and development that found that fetal development can be affected by women taking therapeutic doses of lithium, but that other sources of exposure to lithium do not appear to result in levels that pose a health risk. Their second study, on boric acid, is completed and seeking publication. The IEHR prototype would serve as a good model for Shelby's center, Moore concludes.

### The Right Idea in the Wrong Place?

Carol Maczka disagrees, although she understands how reproductive risk has become a “hot button” issue that needs to be fully addressed. Maczka, director of toxicology and risk assessment at the National Academy of Sciences (NAS), says, “The area of environmental impact on reproduction is exploding. It concerns mothers, it concerns everyone, because it seems to be something that is personally controllable. People are saying that if it is something that I am exposed to, I want to do something about it.”

But Maczka warns that Shelby's center will face difficulties of public misperception and may be the wrong forum in which to address these critical scientific problems. When experts are paid, there is a sense that they are not unbiased. And when commercial interests support such a center, the center can be viewed negatively as a front for industry, says Maczka. John Bucher, a researcher in the NIEHS's Environmental Toxicology Program, says that the experts would be reimbursed for expenses and receive only a nominal payment for their services.

Maczka maintains that only groups like the NAS—which selects its groups of experts through nomination, has peer-reviewed processes, and has a vetting process that involves at least three

reviews—can issue reports that will gain widespread respect and attention. In fact, the NAS has already launched several efforts to study reproductive risk.

One NAS effort, the Board on Environmental Studies and Toxicology, is now reviewing the literature on hormone-related toxicants in the environment to identify known and suspected toxicological mechanisms and impacts on humans, as well as on fish and wildlife. Their multi-partite job is to identify significant uncertainties, limitations of knowledge, and weaknesses in the available evidence; develop a science-based conceptual framework for assessing observed phenomena; and recommend research, monitoring, and testing priorities. The project, expected to cost up to \$900,000, will issue a report in 1997, Maczka says.

A second NAS group, a workshop of experts, is expected to issue an initial report by mid-1996 that focuses on the mechanisms involved in reproductive toxicants. In its second phase, this group will become a committee that will spend 15 months and up to \$800,000 reviewing the data gathered to date, with appropriate public pronouncements to follow.

One scientist on the NAS board wonders how effective any group consensus will be in swaying not only public, but also scientific opinion on reproductive risk. Stephen Safe, a professor of toxicology at Texas A & M University, says that “a lot of researchers' opinions are hardened . . . although I don't have any idea why it is so. All I can predict is that the fervor will continue.”

The EPA's Carole Kimmel, who worked on the IEHR prototype with Moore, counters that the NAS process is good but “incredibly slow.” Furthermore, Kimmel says the Shelby center and the NAS “do not do the same kind of thing. The NIEHS plan calls for evaluation of data on a chemical by chemical basis and is a much more roll-up-your-sleeves type approach.” NAS projects, on the other hand, “look at what new cutting-edge research is related to developmental effects, and how mechanism information is incorporated in risk assessment,” she says.

Kimmel also argues that work with industry representatives was helpful, not harmful, as Maczka suggests. “In many cases, we were able to get information from the industry scientists on the chemicals, exposure, and use that would have been difficult to obtain otherwise,” Kimmel says.

Bucher says that a center such as Shelby proposes is the only way to secure a public trust in the valiant efforts being

made in the nation's labs. “The public should not have to sort through reasonings and regulations,” he says. “It's time to be clear about what the threats are to human reproductive health and happiness, and to move on to preventing them.”

## Phenolphthalein Highlights NTP Bioassay Review



The National Toxicology Program presented six technical reports in the carcinogenesis bioassay series for public review by the NTP's Board of Scientific Counselors' Technical Reports Subcommittee on 5 December 1995. Each report involves a series of long-term studies in which male and female rats and mice were given a range of doses of test chemicals followed by extensive histopathologic examination.

**Phenolphthalein.** Highlighting the meeting were the results for the studies of phenolphthalein, the active ingredient in a variety of over-the-counter laxative preparations and in acid-base indicators. Phenolphthalein exhibited carcinogenic effects when given in the feed at concentrations from 1–5% in rats and 0.3–1.2% in mice. In male rats, there was clear evidence of carcinogenic activity based on the occurrence of adrenal gland pheochromocytomas and adenomas and carcinomas in the kidney. Female rats also had significantly higher incidences of adrenal gland neoplasms in two of the three groups receiving phenolphthalein. There was clear evidence of carcinogenic activity in mice, based on increased incidences of histiocytic sarcomas and malignant lymphomas in both males and females, and ovarian tumors in females.

**Tetrafluoroethylene.** Tetrafluoroethylene is used as a propellant in aerosols and as the monomeric precursor of polymeric Teflon coatings. Rats and mice were exposed to atmospheres containing the tetrafluoroethylene monomer at concentrations up to 1250 ppm, and there was clear evidence of carcinogenic activity for all four sets of sex-species studies. Male and female rats had increased incidences of kidney and liver neoplasms, and male and female mice had significantly increased incidences of liver hemangiomas and hemangiosarcomas, hepatocellular neoplasms, and histiocytic sarcomas.

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